Subthalamic Stimulation in Parkinson Disease

Intraoperative Predictive Factors

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Background: High-frequency stimulation of the subthalamic nucleus (STN) is an effective treatment for advanced forms of Parkinson disease. Postoperative improvement of motor parkinsonian disability is known to depend on patient selection and surgical targeting.

Objective: To determine which clinical and electrophysiological variables evaluated during the operation predict the postoperative clinical outcome of patients with Parkinson disease treated by bilateral high-frequency stimulation of the STN.

Methods: Intraoperative clinical and electrophysiological data obtained in 41 patients with Parkinson disease who underwent bilateral implantation of electrodes for STN stimulation were correlated with the improvement in parkinsonian disability assessed 6 months after the operation.

Results: The extent of STN neuronal activity recorded along the trajectory of the therapeutic electrode had no effect on the postoperative clinical outcome. The intraoperative improvement in segmental akinesia, but not rigidity, was predictive of the postoperative improvement in parkinsonian motor disability and reduction in daily levodopa-equivalent dosage. Parkinsonian motor disability scores assessed after surgery were lower in patients with intraoperative stimulation-induced dyskinesias than in those without stimulation-induced dyskinesias.

Conclusion: The improvement of segmental akinesia and the observation of dyskinesias provoked by stimulation during the operation predict the best postoperative effects of bilateral STN stimulation on parkinsonian motor disability.

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METHODS

PATIENTS

The intraoperative and postoperative clinical characteristics of 61 patients with PD consecutively operated on for bilateral placement of stimulating electrodes within the STN between May 1, 1996, and December 31, 2000, were retrospectively analyzed. Intraoperative data were missing in 18 patients because of general anesthesia (n = 6) or unreported data (n = 12), and postoperative data were missing in 2 patients because of death (n = 1) or absence of clinical evaluation (n = 1). Intraoperative and postoperative data were therefore available in 41 patients (25 men and 16 women; mean ± SD age, 56.0 ± 8.2 years) with advanced forms of the disease (mean ± SD dis-
ease duration, 14.0±5.1 years). Following the administration of a single dose of levodopa (30 mg more than the usual morning dosage of levodopa), parkinsonian motor disability scores (Unified Parkinson’s Disease Rating Scale [UPDRS] part III) improved by a mean ± SD of 74%±15%. Despite optimized drug treatment based on a combination of levodopa and dopamine agonists (mean ± SD daily dosage of levodopa-equivalent, 1349±639 mg), all patients had disabling motor fluctuations and levodopa-induced abnormal involuntary movements (UPDRS part IV, 11.2±3.4). None of the patients had cognitive decline, major depression, or significant abnormalities on brain magnetic resonance imaging, and all patients gave informed written consent for the operation.

Neurosurgical Procedure

The STN was visualized directly on multiplanar reformatted coronal T2-weighted images. The coordinates of the center of the nucleus were first determined using the T2-weighted images with respect to the posterior and anterior commissures and then transcribed to the stereotactic coordinates of the Leksell frame using 3-dimensional T1-weighted acquisition. The procedure began with the right hemisphere. A double oblique extraventricular trajectory was used to avoid blood vessels visualized by 3-dimensional preoperative angiographic magnetic resonance imaging. Surgery was performed under local anesthesia. Neuronal activity was recorded, and the effects of high-frequency (130 Hz, 70 microseconds) stimulation were assessed through 24 stereo-electrodes exploring a volume of 250 mm³ around the magnetic resonance imaging–defined target. The effects of stimulation on parkinsonian features were evaluated according to UPDRS part III criteria. Rigidity was assessed by evaluating changes in passive resistance to active displacement of the wrist at rest (item 22b-c, UPDRS part III). Segmental akinesia was evaluated and scored by estimating the repetitive finger movements (item 23, UPDRS part III). Any stimulation-induced dyskinesias were noted. The optimal functional target was defined by the electrode trajectory that displayed a typical pattern of electrical activity and the effectiveness with which the lowest intensity stimulation (<3 mA) decreased segmental akinesia (item 23), rigidity (item 22b-c), or tremor (item 20b-c, UPDRS part III) without inducing disabling adverse effects. The definitive quadripolar electrode (model 3389-28; Medtronic, Minneapolis, Minn) was implanted bilaterally during the same surgical session. The electrodes were connected to a subcutaneous programmable pulse generator (ITREL II [n=23] and Kineta [n=16]; Medtronic) in the subclavicular area. The therapeutic contacts were fine-tuned by telemetry to achieve continuous stimulation.

Clinical Evaluation

Patients were evaluated 1 month before and 6 months after surgery. Activities of daily living (ADL) (UPDRS part II) were scored during an interview evaluating the state of patients in the off and on drug conditions. Before surgery, evaluation of the motor disability score (UPDRS part III) was performed in the off-drug state as defined by the Core Assessment Program for Surgical Intervventional Therapies in Parkinson’s Disease (ie, after ≥12 hours’ interruption of antiparkinsonian medication) and in the best on-drug condition (“residual” motor disability score) after the administration of a single suprathreshold dose of levodopa (50 mg higher than the usual effective dosage taken in the morning). The akinesia score was defined as the sum of the following motor subscores: facial hypomimia, upper and lower limb akinesia, and body bradykinesia (items 19, 23-26, and 31 of the UPDRS part III). The axial score was defined as the sum of the following motor sub

RESULTS

The data analyzed were those obtained while stimulating the track along which the definitive electrodes were inserted. The effects of continuous bilateral STN stimulation on parkinsonian symptoms were evaluated using a Wilcoxon signed rank test to compare scores obtained before and after surgery. A Spearman rank correlation analysis was used to determine the relationships between the extent of the STN along the therapeutic electrode (ie, the distance over which activity typical of the STN was recorded) and the intraoperative improvement of the parkinsonian symptoms and the postoperative clinical outcome. A nonparametric Kruskal-Wallis test was performed to determine whether the occurrence of intraoperative stimulation-induced dyskinesias affected the postoperative clinical outcome and whether the preoperative clinical characteristics of patients (age, disease duration, severity of the parkinsonian motor disability, and response of parkinsonian motor disability to levodopa) affected the occurrence of intraoperative stimulation-induced dyskinesias. Statistical analyses were performed with the SAS statistical software package, version 8.1 (SAS Institute Inc, Cary, NC), and P<.05 was considered statistically significant (a Bonferroni correction was applied, if necessary).

EFFECTS OF STIMULATION ON PARKINSONIAN MOTOR DISABILITY

Before surgery, antiparkinsonian medication improved the ADL score by 73% (Table 1). Six months after surgery, the ADL score was improved by 61% when patients were receiving continuous STN stimulation without medication (on stimulation and off drug). The combination of STN stimulation and antiparkinsonian medication (on stimulation and on drug) induced a greater improvement in the ADL score (76%) than that obtained with stimulation alone. Before surgery, there was a 74% improvement in the parkinsonian motor disability score (UPDRS part III) after administration of levodopa. Six months after surgery, bilateral continuous stimulation improved the motor disability score (on stimulation and off-drug condition) by 68%. The combination of STN stimulation and levodopa administration induced a greater motor improvement (86%) than that obtained before surgery with levodopa treatment or after surgery with stimulation alone.
Before surgery, there was a 65% levodopa-induced improvement in the axial motor score. After surgery, the axial score was improved by 64% when the patient was in the on stimulation and off-drug condition. The combination of STN stimulation and levodopa administration induced a greater improvement of the axial score (76%) than that obtained before surgery with levodopa treatment or after surgery with stimulation alone. Following STN stimulation, the levodopa-equivalent dosages were decreased by 74%, whereas the scores for UPDRS part IV, duration of motor fluctuations, and levodopa-induced dyskinesias were improved by 83%, 83%, and 70%, respectively.

**PREDICTORS OF POSTOPERATIVE CLINICAL OUTCOME**

**Stimulation-Induced Improvement in Parkinsonian Symptoms During the Operation**

Typical STN neuronal activity was recorded in 41 patients and in 40 of 41 patients during neurosurgery in the right and left hemispheres, respectively. The mean±SD distance over which typical STN neuronal activity was recorded was used to provide an index of the anatomical extent of the STN along the trajectory of the definitive electrode. This index was 4541±1436 µm (range, 2000-6000 µm) for the right electrodes and 4300±1779 µm (range, 0-7000 µm) for the left electrodes. There was no correlation between the length of microrecording of STN activity and any of the clinical variables estimated 6 months after the operation (at the time of maximal clinical improvement under STN stimulation and levodopa treatment).

Upper limb (wrist) rigidity was improved in 37 of 38 patients during implantation in the right STN and in all 38 patients (ie, those for whom data were available) during implantation in the left STN, but there was no correlation between the intraoperative degree of improvement of rigidity and the postoperative clinical outcome (data not shown). The effects of intraoperative unilateral stimulation of the STN on the segmental akinesia score (repetitive finger movements) were positively correlated with postoperative improvement of akinesia and UPDRS part III scores (on stimulation and on drug) and with the reduction of levodopa-equivalent daily dosage (Table 2). There was no correlation between the intraoperative effect of stimulation on segmental akinesia and the postoperative scores for rigidity, tremor, axial symptoms (ie, gait, speech, postural stability, and posture), motor fluctuations, and levodopa-induced dyskinesias (data not shown). In summary, we found that the greater the intraoperative stimulation-induced improvement in segmental akinesia, the lower the postoperative akinesia and parkinsonian disability scores and levodopa-equivalent daily dosage.

**Presence of Stimulation-Induced Dyskinesias During the Operation**

Following stimulation during the operation, contralateral dyskinesias were observed in 18 of 38 patients (for whom data were available) during electrode implantation in the right STN and in 22 of 35 patients during implantation in the left STN, and 13 patients experienced dyskinesias during implantation.

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**Table 1. Effects of Continuous Bilateral High-Frequency Stimulation of the Subthalamic Nucleus in 41 Patients With Parkinson Disease**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Before Surgery</th>
<th>After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off Drug</td>
<td>On Drug</td>
</tr>
<tr>
<td>UPDRS part II†</td>
<td>25 ± 6.8</td>
<td>7.2 ± 6.4 (73)†</td>
</tr>
<tr>
<td>UPDRS part III†</td>
<td>43.8 ± 17.2</td>
<td>12.2 ± 11.1 (74)†</td>
</tr>
<tr>
<td>Axial score</td>
<td>8.1 ± 3.4</td>
<td>3.0 ± 2.2 (65)†</td>
</tr>
<tr>
<td>Levodopa equivalent, mg/d</td>
<td>NA</td>
<td>1349 ± 639</td>
</tr>
<tr>
<td>UPDRS part IV†</td>
<td>NA</td>
<td>11.2 ± 3.4</td>
</tr>
<tr>
<td>Motor fluctuations</td>
<td>NA</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>Levodopa-induced dyskinesias</td>
<td>NA</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

**Table 2. Relation Between the Intraoperative Effects of Stimulation on Segmental Akinesia and the Postoperative Effects of Stimulation on the Clinical Outcome**

<table>
<thead>
<tr>
<th>Intraoperative Assessment of Finger Taps on Stimulation (Item 23, UPDRS Part III)†</th>
<th>Postoperative Clinical Outcome</th>
<th>Left Finger (Right Lead)</th>
<th>Right Finger (Left Lead)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor disability (UPDRS III)‡</td>
<td>On stimulation and off drug</td>
<td>0.43†</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>On stimulation and on drug</td>
<td>0.52†</td>
<td>0.51†</td>
</tr>
<tr>
<td>Akinesia score</td>
<td>On stimulation and off drug</td>
<td>0.33</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>On stimulation and on drug</td>
<td>0.44†</td>
<td>0.54†</td>
</tr>
<tr>
<td>Levodopa-daily dosage equivalent</td>
<td>On stimulation</td>
<td>0.43†</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not applicable; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Values are mean ± SD (percentage of improvement compared with the off-drug condition before surgery).

†P < .05 compared with the on-drug condition before surgery.

‡P < .05 compared with the on stimulation and off-drug condition after surgery.

§P < .05 compared with the on-drug condition before surgery.

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dyskinesias during implantation in both STN. The spectrum of dyskinesias included dystonic fix posturing combined with repetitive movements, with or without myoclonic bursts of the legs, and choreic movement of the upper limb that could spread to the trunk and then to the rest of the body. Dyskinesias occurred on the side contralateral to stimulation but were also observed on the ipsilateral side. The severity of dyskinesias provoked by intraoperative stimulation increased with the increment of the electrical stimulation current, and vice versa (data not shown). Compared with patients who had no intraoperative dyskinesias, patients with intraoperative stimulation-induced dyskinesias (unilateral, n = 11; and bilateral, n = 13) had significantly lower postoperative parkinsonian motor disability (UPDRS III, on stimulation and on-drug condition), axial (on stimulation and off-drug condition, and on-drug condition), dysarthria (on stimulation and off-drug condition), gait (on stimulation and off-drug condition, data not shown), and motor fluctuations scores (Figure).

Preoperative Clinical Characteristics of Patients

There were no significant differences between patients who experienced intraoperative stimulation-induced dyskinesias and those who did not with respect to the following preoperative characteristics: age, disease duration, levodopa-equivalent daily dosage, preoperative severity of motor fluctuations, and levodopa-induced dyskinesias. However, patients who experienced intraoperative stimulation-induced dyskinesias during implantation of electrodes in both STNs had a better preoperative response of axial symptoms (P < .05) and tended to have a better preoperative response of parkinsonian motor disability (UPDRS part III) (P = .06) to levodopa compared with those without intraoperative dyskinesias (data not shown).

In a selected sample of patients with PD responsive to levodopa, we found that the best predictors of the postoperative clinical outcome were the improvement of segmental akinesia, but not rigidity, and the occurrence of unilateral or bilateral dyskinesias provoked by stimulation of the therapeutic target during the operation.

No correlation was found between the distance over which typical STN neuronal activity was recorded (ie, the extent of the STN along the implanted electrode) and the postoperative clinical outcome, suggesting that implantation of electrodes based solely on micorecording may fail to provide optimal results. This lack of correlation could result from a statistical bias, however, as neuronal activity characteristic of the STN was recorded bilaterally in 40 of the 41 patients studied, thus confirming the quality of the targeting based on direct visualization of the STN.9

Intraoperative stimulation-induced improvement in segmental akinesia was predictive of the postoperative improvement of parkinsonian motor disability score, including akinesia, and of the reduction of levodopa-equivalent dosage (Table 2). The assessment of repetitive finger movements during the operation thus appears to be a useful maneuver, although its significance likely decreases with the duration of the procedure because of patient fatigue. In contrast, improvement of rigidity was not a predictive factor of the postoperative clinical outcome, probably because rigidity was improved in almost all patients. This suggests that rigidity is alleviated irrespective of the site of stimulation within the area of the STN, including surrounding structures such as the zona incerta,14 external and internal pallidum,15 and thalamus.16 According to this study, intraoperative evaluation of changes in rigidity cannot, therefore, be considered as an essential criterion for electrode implantation. A robust postoperative therapeutic effect on the severity of motor fluctuations and parkinsonian motor disability (in particular, gait and speech disorders) was obtained when electrodes were inserted along the track where intraoperative stimulation induced dyskinesias. This is in line with a previous study17 suggesting that the site of optimal lesion was indicated by the occurrence of stimulation-induced dyskinesias in patients with PD treated by pallidotomy. These stimulation-induced dyskinesias may be underestimated when they present as painful fixed postures reminiscent of biphasic dyskinesias,18 which then evolve toward a monophasic pattern of dyskinesias while the electric current is increased.19 The results therefore suggest that the best target for implantation of therapeutic electrodes during the operation can be predicted from the occurrence of stimulation-induced dyskinesias, ie, at the site of maximal inactivation of the STN.20 The fact that intraoperative stimulation-induced dyskinesias were obtained in patients responsive to levodopa treatment confirms that the results of neurosurgery become optimal in patients selected for an excellent response to levodopa treatment, namely, those with severe and selective dopaminergic brain lesions.7
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